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TITLE: Early Recognition of Chronic Traumatic Encephalopathy Through FDDNP PET Imaging

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Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio

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**14. ABSTRACT**

1. The PET biomarker, F-FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl(methyl)amino]-2-naphthyl} ethylidene) malononitrile) [FDDNP] has shown sensitivity for in vivo detection of tau i addition to □-sheet-containing brain amyloid neuroaggregates. Tau protein in a characteristic distribution is felt to be the cardinal pathologic feature of Chronic Traumatic Encephalopathy. This project will examine whether FDDNP PET imaging correlat with, and/or can predict, decline in cognitive function in those exposed to cumulative head trauma.

**15. SUBJECT TERMS**
Traumatic Brain Injury
Positron Emission Tomography

| 16. SECURITY CLASSIFICATION OF: | | | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES | 19a. NAME OF RESPONSIBLE PERS |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRMC |
| Unclassified | Unclassified | Unclassified | Unclassified | 9 | 19b. TELEPHONE NUMBER *(include a code)* |

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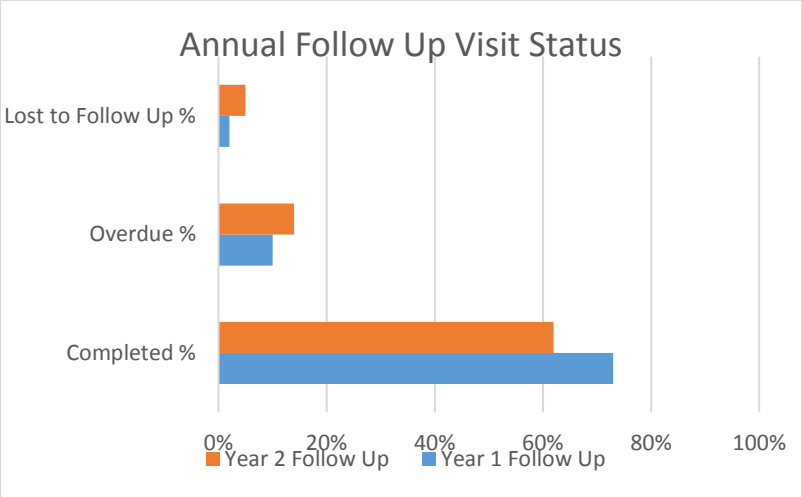
**1. Introduction:** Blast injuries and other head injuries sustained in battle have been associated with the development of chronic traumatic encephalopathy (CTE). Pathological series have indicated that a characteristic feature of CTE is accumulation of tau protein in the brain. Until very recently, there has been no reliable way of measuring tau deposition in the brain during life. One PET biomarker, F-FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl(methyl)amino]-2-naphthyl} ethylidene) malononitrile) [FDDNP] has shown sensitivity for in vivo detection of tau in addition to B-sheet-containing brain amyloid neuroaggregates. This project will examine whether FDDNP PET imaging correlates with, and/or can predict, decline in cognitive function in those exposed to cumulative head trauma.

**2. Keywords:** Traumatic Brain Injury, Chronic Traumatic Encephalopathy, PET imaging, Tau

**3. Accomplishments:**

*Major goals*: Upon receiving approval from the Human Research Protection Office, enrollment of participants began in March, 2015. The major goal for 2017 was to complete enrollment; we finished enrollment in October, 2017, having completed 68 PET FDDNP studies.

*Major accomplishments*: Each subject is to be followed yearly for 3 years as part of the Professional Fighters Brain Health Study. Retention rate has been excellent. As of November, 2017 we have only 2 subjects who have been lost to follow up due to moving out of the country. Because of rolling enrollment over multiple years, follow up visits are staggered. The graph below indicates the number of subjects that have completed follow up visits, and the number who are overdue for their follow up ( the reason the percentages do not add up to 100 is that some participants are not yet due for these follow ups). We are beginning to see our 3 year follow up visits now and the projected time for completion of all 3 year follow up visits is 4$^{th}$ quarter, 2020.




Interim analysis of data collected by the 3rd quarter of 2016 have been presented at two conferences in 2017 (see below). Using the automated MIAKAT (Imanova) kinetic analysis software, parametric images of distribution volume ratio (DVR) were generated with the cerebellum as the reference region. Regional DVR measurements were obtained using the built-in brain template with gray mask applied. 38 participants were included in the analysis (34 fighters, 4 controls) The results indicate a relationship between increased exposure to head trauma (measured by number of fights) and increased FDDNP uptake in the amygdala and other temporal lobe structures. However, uptake in these structures was also associated with age.

Table 1 - Regional uptake in ROIs with Age, Years of Pro Fighting, and Number of Pro Fights (Pearson's correlations; ns – non significant)

| Table 2: Uptake and exposure | Age | Years of Fighting | Number of Fights |
|---|---|---|---|
| amygdala, | .376* | ns | .412* |
| hippocampus | .330* | ns | .356* |
| parahippocampal gyrus | .ns | ns | .396* |
| brainstem | ns | ns | ns |
| temporal | .337* | ns | .434* |
| posterior cingulate | ns | ns | .346* |
| parietal | ns | ns | Ns |
| thalamus | ns | -.379* | Ns |
| basal ganglia | ns | ns | .391* |

From these results, it became clear that age is an important modifying factor in interpreting PET FDDNP images; further analyses were postponed until we finished enrollment, which included additional older control subjects.

67 scans (49 fighters, 19 controls) have now been processed using automated PMOD software ( one scan was not usable). The DVR results include PET motion correction and PET partial volume correction. We are currently running analyses examining correlations with PET regional uptake, exposure measures, and baseline MRI and clinical outcomes, controlling for age, race and education).

*Training opportunities*: This project has provided a training opportunity for our post –doctorate student, Bern Lee, who has worked on assessing the relationship between FDDNP imaging results and neuropsychological measures.

*Dissemination of Results*: Nothing to report

*Future plans*: Over the next 12 months, the investigators will be able to complete the one year follow ups on the entire cohort and complete two year follow up on close to two thirds of the cohort; we will have 3 year data on some subjects.. In addition, further interim analyses will be conducted to evaluate the correlations between:

- FDDNP PET binding and change over 1 or 2 year periods in clinical and imaging measures
- FDDNP PET binding and certain risk factors ( extent of exposure to head trauma, genetics)
- FDDNP PET binding and multimodal MRI measures ( in collaboration with ADMdx)
- FDDNP PET binding compared to AV 1451 ,another PET tau tracer that has been done on a subset of the cohort ( in collaboration with Banner Alzheimer's Institute)
- Association between clinician visual reads of the FDDNP scans and clinical status of the subject

4**. Impact:**

*Impact on development of principal disciplines*: At the current stage, the impact from this project is limited. However, the publication by Dr. Omalu and his group that reported the correlation between PET FDDNP binding and post-mortem findings in a retired NFL player has raised attention to this imaging method (Omalu B, et al. Postmortem Autopsy-Confirmation of Antemortem [F-18]FDDNP-PET Scans in a Football Player With Chronic Traumatic Encephalopathy. Neurosurgery. **2017** Nov 10. Epub ahead of print). In the case study, [F-18]FDDNP-PET binding levels correlated with brain tau deposition (rs = 0.59, P = .02), with highest relative distribution volumes in the parasagittal and paraventricular regions of the brain

and the brain stem. Our study is one of the largest series using PET FDDNP imaging in individuals exposed to repetitive head trauma and followed over time. This puts the study in position to determine if certain binding patterns correlate with clinical symptoms and brain structural imaging over time.

*Impact on other disciplines*: Nothing to report

*Impact on technology transfer*: Nothing to report

*Impact on society beyond science:* Nothing to report

5 **Changes/Problems:**

*Changes in approach*: No changes in approach to report

*Problems or delays:* the major problem/delay that has occurred in this study has been the slow rate of recruitment. In 2017, we completed recruitment and all baseline FDDNP scans. We have r received a no cost extension for 2018 to allow for the ongoing follow up of the cohort, as some of the most impactful information will be gained by determining the clinical and radiological trajectory of the subjects and the correlation with baseline PET FDDNP imaging

*Changes that impact expenditures*: None

*Changes in care of human subjects*: None. The study has received ongoing approval by the Cleveland Clinic IRB through 12/2/18.

6**. Products:**

The following conference presentations have been presented at national conferences:

***Sarah J. Banks, Vladimir Kepe, Frank P. DiFilippo, Bern Lee Jorge Barrio, and Charles Bernick*. Regional FDDNP Uptake and Exposure to Professional Fighting (Human Amyloid Imaging, Miami, 1/17)**

***Bern G. Lee, Charles Bernick, Vladimir Kepe, Frank P. DiFilippo, & Sarah J. Banks***. **[F-18]FDDNP Uptake, Neurocognition, and Number of Fights in Professional Boxers and MMA fighters (International Neuropsychology Society, New Orleans, 2/17)**

No other products resulted from this study over the last year.

7. **Participants and other Collaborating Organizations**

The individuals who have worked on this project include:

Charles Bernick – no change

Sarah Banks – no change

Jorge Barrio - no change

Pamela Dino

Project role: research coordinator

Person month worked: 4

Contributions to project: Subject scheduling, conduct of study visit

Funding support – Cleveland Clinic

*Change in active support*: Nothing to report

Other organizations:

ADMdx, Chicago, Ill

Contribution: Analyses and interpretation of PET FDDNP imaging using machine learning methods and multimodal approaches.

Financial support: In – kind contribution of their staff time and facilities to analyze PET FDDNP images

## 8. Quad Chart:

**Early Recognition of CTE through PET FDDNP Imaging**
PT120134

**PI: Charles Bernick  Org: Cleveland Clinic  Award Amount: $746,068**

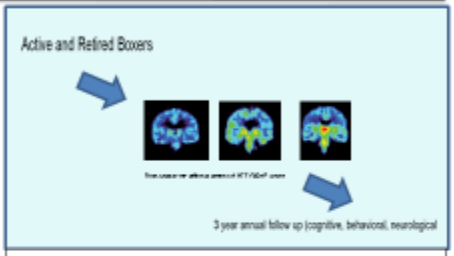
### Study/Product Aim(s)

•**Study**: Exam the performance of PET FDDNP in a group of active and retired professional boxers and non trauma exposed controls.

•**Outcomes**: To determine if PET FDDNP imaging may be a potential biomarker of and diagnostic tool for CTE

### Approach

- Cohort derived from the Professional Fighters Brain Health Study
- Active and retired boxers , both cognitively normal and cognitively impaired
- Subjects undergo baseline PET FDDNP imaging and followed annually with cognitive, behavioral, and neurological testing x2.




### Timeline and Cost

| Activities | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|
| Baseline PET FDDNP | | | | | | |
| Annual MRI, cognitive, behavioral assessments | | | | | | |
| Analysis | | | | | | |
| | | | | | | |
| **Estimated Budget ($K)** | $304 | $302 | $140 | $0 | $0 | $0 |

**Goals/Milestones**

**CY13 Goal** – Develop SOP and train coordinator
IRB Submission
Finalize logistics of transfer of FDDNP from production to site
**CY14 Goals** - IRB approval obtained
HRPO approval obtained
Identified eligible subjects
**CY15 Goal** – Enrollment of subjects, 1st subject enrolled 3/15
**CY16 Goal** – Continue enrollment and begin annual follow up visits, analyses
**CY 17 Goal** - Complete enrollment and continue annual follow up visits, analyses
**CY 20 Goal** - Complete 3 year follow up visits on all subjects

**Comments/Challenges/Issues/Concerns**

- Delay in completion of service agreement/IRB approval/HRPO approval delayed initial enrollment; PET FDDNP imaging began 3/15. MRI scanner replacement slowed 2016 enrollment.